AVAC
AIDS Vaccine Advocacy Coalition
Advocacy to accelerate ethical research & global delivery of AIDS vaccines

September 7, 2004

U.S. Food and Drug Administration
Division of Dockets Management
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RE: **Docket No. 2004N-0018;** Human Subject Protection – Foreign Clinical Studies Not Conducted Under an Investigational New Drug (IND) Application – Proposed Rule – 69 Fed. Reg. 32467, June 10, 2004

To the Food and Drug Administration:

The AIDS Vaccine Advocacy Coalition (AVAC) is a volunteer and nonprofit organization dedicated to ethical research and global delivery of AIDS vaccines. We are pleased to submit these comments regarding FDA's proposed rule on acceptance of foreign clinical studies not conducted under an IND as support for an IND or marketing application for a drug or biological product. FDA proposes to replace the existing requirement that such studies be conducted in accordance with ethical principles found in the Declaration of Helsinki (Declaration)[1] or the laws and regulations of the country in which the research is conducted with a requirement that the studies be conducted in accordance with good laboratory practice (GCP) and with review and approval by an independent ethics committee.

AVAC objects to the deletion of reference for the Declaration in the acceptance of such studies. In effect, the deletion would remove opportunity to direct at least two substantive matters in the conduct of ethical trials – use of placebos when other approved therapy is available and access to the benefits and results of the research human subject participants are recruited to

[1] http://www.wma.net/e/policy/pdf/17c.pdf The Declaration was last amended in 2000; paragraph 29 was further explained in 2002. FDA has stated that its current 21 C. F.R. Part 312 regulations have not kept pace with these later Declaration amendments and that only the 1989 version of the Declaration is adopted in existing requirements. FDA, Guidance for Industry: Acceptance of Foreign Clinical Studies (2001) http://www.fda.gov/cder/guidance/fstud.pdf

study.[2] That would be the consequence if the proposal is adopted because the Declaration addresses those matters while GCP may be silent on them.[3]

We recognize that there has been uncertainty as to the scope of the Declaration's impact on these substantive matters or the best way to implement them for the benefit of research subjects.[4] The way to resolve that uncertainty is to clarify their scope in public discussion not delete the requirements altogether or fail to keep pace with the Declaration's provisions as it is amended by the world community. A deletion would imply, for example, that FDA thinks non-US study populations do not need access to results or imply that non-US populations could be studied and put at risk only to identify medical products that would benefit the US population. We assume that is not FDA's intention. Clinical trials should be conducted in populations that stand to benefit in relation to the risks they incur from study.

These two matters have been examined by authoritative organizations including, among others, the National Bioethics Advisory Commission (NBAC), the Joint United Nations Programme on HIV/AIDS, and the Nuffield Council on Bioethics.[5] Without summarizing each of these authorities extensively, it may be helpful to remind FDA of the views of the NBAC chairs. They stated after report publication:

> An experimental intervention should normally be compared with an established, effective treatment (defined as a treatment that has widespread acceptance by the medical profession throughout the world and that is as effective as any alternative treatment for the disease or condition), whether or not that treatment is available in the host country. Therefore, the presumption is that a placebo control, or any other control that is less effective than an established, effective treatment, is not ethically acceptable. However, we would permit an exception in a situation in which the only useful research design,

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[2] The two matters are addressed in Declaration paragraphs 29 and 30, added in 2000. They state:

> *29.* The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
> 30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

[3] The proposed rule preamble mentions that GCP placebo guidance that FDA intends to incorporate in regulations may include the International Conference on Harmonisation (ICH) "E10 Choice of Control Group and Related Issues in Clinical Trials" guidance (69 Fed. Reg. 32468, fn. 1). However, it is unclear from the text of proposed revised 21 C.F.R. §312.120 which ICH guidance would be formally adopted (69 Fed. Reg. 32474-5). The ICH E10 guidance (http://www.fda.gov/cder/guidance/4155fnl.pdf)may be compatible with Declaration paragraph 29. If the proposal moves forward to final, we request that FDA specify in §312.120 that both guidance directions – Declaration paragraph 29 and E10 - are incorporated in codified regulations, along with other ICH guidance documents. GCP guidelines appear to be silent on Declaration paragraph 30 issues.

[4] See, for example, Ananworanich, J;Cheunyam, T; Teeratakulpisarn, S; Boyd, M;Ruxrungtham, K; Lange, J; Cooper, D; Phanuphak, P.Creation of a drug fund for post-clinical trial access to antiretrovirals. Lancet 2004; **364**: 101–02. http://pdf.thelancet.com/pdfdownload?uid=llan.364.9428.review_and_opinion.30156.1&x=x.pdf

[5] Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries http://www.georgetown.edu/research/nrcbl/nbac/clinical/Vol1.pdf; Ethical Considerations in HIV Preventive Vaccine Research (2004) – downloadable from: http://www.unaids.org/en/resources/publications.asp; The Ethics of Research Related to Health Care in Developing Countries (2002) http://www.nuffieldbioethics.org/filelibrary/pdf/errhdc_fullreport.pdf

from the host country's perspective, required a less effective intervention in the control group, if the condition being studied was not life-threatening and if the trial received approval from an ethics review committee in the host country as well as one in the United States. ....An exception should be limited and should not be extended to trials that fail to meet these requirements and qualifications. It would not apply to the treatment of life-threatening diseases such as HIV infection. If our standard were adopted, many trials currently under way or in the planning stages might have to be stopped or redesigned...

Making a successful new intervention available to participants after a trial is an especially important ethical obligation.... In addition, we believe that research participants should not be made worse off as a result of their inability to have continued access to the successful intervention after the trial has ended. ...Trust in the medical profession is central to anyone's willingness to participate in a trial. Any sense of abandonment is difficult to address adequately in the informed-consent process. A plan for the routine provision of a successful new intervention to participants after a trial has been completed is one way to ensure that the study is responsive to the health needs of the host country. The ethical obligation to provide the intervention to others in the community who might benefit from it is considerably less strong, but a plan to do so would help reduce the risk of exploitation.[6]

We do not minimize the practical difficulties involved to achieve these ethical standards, but we also do not support avoiding their implementation in clinical trials by eliminating or failing to adopt relevant requirements. The approval and study of medical products is increasingly a global harmonized effort that requires substantial interaction between and consideration for all affected populations. In the case of global pandemics such as HIV/AIDS, it is impossible to predict the complete set of multi-center data needed to approve products in any country. US regulations – the backbone of US policy to export approved products to fight this disease - should raise the bar of ethical standards applicable in all locations when they can.

For similar reasons, we also object to the proposed deletion of the standards currently found in 21 C.F.R §312.120(a) and (c), that trials must be "conducted in accordance with ethical principles acceptable to the world community" and, if not using the Declaration, the "laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual." FDA's proposal would eliminate both of these criteria for acceptance of data. Although the proposed rule references general GCP standards, the text of the revised §312.120 does not clarify whether GCP as interpreted by the host country is at all relevant to acceptance of data or whether the ethics committee that must be used is one approved by the host country.

AVAC supports the proposed requirement for GCP and the intention to ensure and improve the quality of data obtained from studies. Many elements of GCP overlap and are

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[6] Shapiro HT and Meslin, EM. Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries. New England Journal of Medicine 2001; **345**: 139-141.

entirely consistent with principles in the Declaration. To that extent, the two are harmonious and the IND regulations are improved by including both.

In conclusion, AVAC requests that FDA withdraw the proposed regulation and commence practical discussion to harmonize the latest version of Declaration principles and improved data integrity features of GCP. We appreciate this opportunity to comment. Please contact either Mitchell Warren (tel: 212-367-1084; email: mitchell@avac.org) or Robert Reinhard (tel: 415-268-7469; email: rreinhar@mofo.com) for more information or if you have any questions.

Sincerely,

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Board Member, AVAC

CC: David A. Lepay, FDA